



## spinal muscular atrophy

Spinal muscular atrophy is a genetic disorder that affects the control of muscle movement. It is caused by a loss of specialized nerve cells, called motor neurons, in the spinal cord and the part of the brain that is connected to the spinal cord (the brainstem). The loss of motor neurons leads to weakness and wasting (atrophy) of muscles used for activities such as crawling, walking, sitting up, and controlling head movement. In severe cases of spinal muscular atrophy, the muscles used for breathing and swallowing are affected. There are many types of spinal muscular atrophy distinguished by the pattern of features, severity of muscle weakness, and age when the muscle problems begin.

Type I spinal muscular atrophy (also called Werdnig-Hoffman disease) is a severe form of the disorder that is evident at birth or within the first few months of life. Affected infants are developmentally delayed; most are unable to support their head or sit unassisted. Children with this type have breathing and swallowing problems that may lead to choking or gagging.

Type II spinal muscular atrophy is characterized by muscle weakness that develops in children between ages 6 and 12 months. Children with type II can sit without support, although they may need help getting to a seated position. Individuals with this type of spinal muscular atrophy cannot stand or walk unaided.

Type III spinal muscular atrophy (also called Kugelberg-Welander disease or juvenile type) has milder features that typically develop between early childhood and adolescence. Individuals with type III spinal muscular atrophy can stand and walk unaided, but walking and climbing stairs may become increasingly difficult. Many affected individuals will require wheelchair assistance later in life.

The signs and symptoms of type IV spinal muscular atrophy often occur after age 30. Affected individuals usually experience mild to moderate muscle weakness, tremor, twitching, or mild breathing problems. Typically, only muscles close to the center of the body (proximal muscles), such as the upper arms and legs, are affected in type IV spinal muscular atrophy.

The features of X-linked spinal muscular atrophy appear in infancy and include severe muscle weakness and difficulty breathing. Children with this type often have joint deformities (contractures) that impair movement. In severe cases, affected infants are born with broken bones. Poor muscle tone before birth may contribute to the contractures and broken bones seen in these children.

Spinal muscular atrophy, lower extremity, dominant (SMA-LED) is characterized by leg muscle weakness that is most severe in the thigh muscles (quadriceps). This weakness

begins in infancy or early childhood and progresses slowly. Affected individuals often have a waddling or unsteady walk and have difficulty rising from a seated position and climbing stairs.

An adult-onset form of spinal muscular atrophy that begins in early to mid-adulthood affects the proximal muscles and is characterized by muscle cramping of the limbs and abdomen, weakness in the leg muscles, involuntary muscle contractions, tremors, and a protrusion of the abdomen thought to be related to muscle weakness. Some affected individuals experience difficulty swallowing and problems with bladder and bowel function.

## Frequency

Spinal muscular atrophy affects 1 in 6,000 to 1 in 10,000 people.

## Genetic Changes

Mutations in the *SMN1*, *UBA1*, *DYNC1H1*, and *VAPB* genes cause spinal muscular atrophy. Extra copies of the *SMN2* gene modify the severity of spinal muscular atrophy.

The *SMN1* and *SMN2* genes provide instructions for making a protein called the survival motor neuron (SMN) protein. The SMN protein is important for the maintenance of specialized nerve cells called motor neurons. Motor neurons are located in the spinal cord and the brainstem; they control muscle movement. Most functional SMN protein is produced from the *SMN1* gene, with a small amount produced from the *SMN2* gene. Several different versions of the SMN protein are produced from the *SMN2* gene, but only one version is full size and functional.

Mutations in the *SMN1* gene cause spinal muscular atrophy types I, II, III, and IV. *SMN1* gene mutations lead to a shortage of the SMN protein. Without SMN protein, motor neurons die, and nerve impulses are not passed between the brain and muscles. As a result, some muscles cannot perform their normal functions, leading to weakness and impaired movement.

Some people with type II, III, or IV spinal muscular atrophy have three or more copies of the *SMN2* gene in each cell. Having multiple copies of the *SMN2* gene can modify the course of spinal muscular atrophy. The additional SMN proteins produced from the extra copies of the *SMN2* gene can help replace some of the SMN protein that is lost due to mutations in the *SMN1* gene. In general, symptoms are less severe and begin later in life as the number of copies of the *SMN2* gene increases.

Mutations in the *UBA1* gene cause X-linked spinal muscular atrophy. The *UBA1* gene provides instructions for making the ubiquitin-activating enzyme E1. This enzyme is involved in a process that targets proteins to be broken down (degraded) within cells. *UBA1* gene mutations lead to reduced or absent levels of functional enzyme, which disrupts the process of protein degradation. A buildup of proteins in the cell can cause it to die; motor neurons are particularly susceptible to damage from protein buildup.

The *DYNC1H1* gene provides instructions for making a protein that is part of a group (complex) of proteins called dynein. This complex is found in the fluid inside cells (cytoplasm), where it is part of a network that moves proteins and other materials. In neurons, dynein moves cellular materials away from the junctions between neurons (synapses) to the center of the cell. This process helps transmit chemical messages from one neuron to another. *DYNC1H1* gene mutations that cause SMA-LED disrupt the function of the dynein complex. As a result, the movement of proteins, cellular structures, and other materials within cells are impaired. A decrease in chemical messaging between neurons that control muscle movement is thought to contribute to the muscle weakness experienced by people with SMA-LED. It is unclear why this condition affects only the lower extremities.

The adult-onset form of spinal muscular atrophy is caused by a mutation in the *VAPB* gene. The *VAPB* gene provides instructions for making a protein that is found in cells throughout the body. Researchers suggest that this protein may play a role in preventing the buildup of unfolded or misfolded proteins within cells. It is unclear how a *VAPB* gene mutation leads to the loss of motor neurons. An impaired *VAPB* protein might cause misfolded and unfolded proteins to accumulate and impair the normal function of motor neurons.

Other types of spinal muscular atrophy that primarily affect the lower legs and feet and the lower arms and hands are caused by the dysfunction of neurons in the spinal cord. When spinal muscular atrophy shows this pattern of signs and symptoms, it is also known as distal hereditary motor neuropathy. The various types of this condition are caused by mutations in other genes.

## **Inheritance Pattern**

Types I, II, III, and IV spinal muscular atrophy are inherited in an autosomal recessive pattern, which means both copies of the *SMN1* gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Extra copies of the *SMN2* gene are due to a random error when making new copies of DNA (replication) in an egg or sperm cell or just after fertilization.

SMA-LED and the late-onset form of spinal muscular atrophy caused by *VAPB* gene mutations are inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

X-linked spinal muscular atrophy is inherited in an X-linked pattern. The *UBA1* gene is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected

by X-linked disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

### **Other Names for This Condition**

- hereditary motor neuronopathy
- progressive muscular atrophy
- SMA
- spinal amyotrophy

### **Diagnosis & Management**

#### Genetic Testing

- Genetic Testing Registry: Adult proximal spinal muscular atrophy, autosomal dominant  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1866777/>
- Genetic Testing Registry: Arthrogryposis multiplex congenita, distal, X-linked  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1844934/>
- Genetic Testing Registry: Kugelberg-Welander disease  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0152109/>
- Genetic Testing Registry: Spinal muscular atrophy type 4  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1838230/>
- Genetic Testing Registry: Spinal muscular atrophy, lower extremity predominant 1, autosomal dominant  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1834690/>
- Genetic Testing Registry: Spinal muscular atrophy, type II  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0393538/>
- Genetic Testing Registry: Werdnig-Hoffmann disease  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0043116/>

#### Other Diagnosis and Management Resources

- GeneReview: Spinal Muscular Atrophy  
<https://www.ncbi.nlm.nih.gov/books/NBK1352>
- GeneReview: Spinal Muscular Atrophy, X-Linked Infantile  
<https://www.ncbi.nlm.nih.gov/books/NBK2594>

- Genomics Education Programme (UK)  
<https://www.genomicseducation.hee.nhs.uk/resources/genetic-conditions-factsheets/item/87-spinal-muscular-atrophy-type-1>
- MedlinePlus Encyclopedia: Spinal Muscular Atrophy  
<https://medlineplus.gov/ency/article/000996.htm>

#### General Information from MedlinePlus

- Diagnostic Tests  
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy  
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling  
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care  
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation  
<https://medlineplus.gov/surgeryandrehabilitation.html>

### **Additional Information & Resources**

#### MedlinePlus

- Encyclopedia: Spinal Muscular Atrophy  
<https://medlineplus.gov/ency/article/000996.htm>
- Health Topic: Spinal Muscular Atrophy  
<https://medlineplus.gov/spinalmuscularatrophy.html>

#### Genetic and Rare Diseases Information Center

- Spinal muscular atrophy  
<https://rarediseases.info.nih.gov/diseases/7674/spinal-muscular-atrophy>
- Spinal muscular atrophy 1  
<https://rarediseases.info.nih.gov/diseases/7883/spinal-muscular-atrophy-1>
- Spinal muscular atrophy type 2  
<https://rarediseases.info.nih.gov/diseases/4945/spinal-muscular-atrophy-type-2>

#### Additional NIH Resources

- National Institute of Neurological Disorders and Stroke  
<https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Spinal-Muscular-Atrophy-Fact-Sheet>

## Educational Resources

- Boston Children's Hospital  
<http://www.childrenshospital.org/conditions-and-treatments/conditions/spinal-muscular-atrophy-sma>
- Children's Hospital of The King's Daughters  
<http://www.chkd.org/Patients-and-Families/Health-Library/Content.aspx?ContentTypeId=90&contentId=P02623>
- Cure SMA: The Genetics of Spinal Muscular Atrophy  
<http://www.curesma.org/documents/support--care-documents/genetics-of-sma.pdf>
- Cure SMA: Understanding Spinal Muscular Atrophy  
<http://www.curesma.org/documents/support--care-documents/understanding-sma.pdf>
- Disease InfoSearch: Spinal muscular atrophy  
<http://www.diseaseinfosearch.org/Spinal+muscular+atrophy/6729>
- Disease InfoSearch: Spinal muscular atrophy 1  
<http://www.diseaseinfosearch.org/Spinal+muscular+atrophy+1/6731>
- Disease InfoSearch: Spinal muscular atrophy type 2  
<http://www.diseaseinfosearch.org/Spinal+muscular+atrophy+type+2/6735>
- Indiana University, International SMA Patient Registry  
<https://smaregistry.iu.edu/>
- MalaCards: spinal muscular atrophy  
[http://www.malacards.org/card/spinal\\_muscular\\_atrophy](http://www.malacards.org/card/spinal_muscular_atrophy)
- Merck Manual Home Edition for Patients and Caregivers  
<http://www.merckmanuals.com/home/brain-spinal-cord-and-nerve-disorders/peripheral-nerve-disorders/spinal-muscular-atrophies>
- My46 Trait Profile  
<https://www.my46.org/trait-document?trait=Spinal%20muscular%20atrophy&type=profile>
- Orphanet: Proximal spinal muscular atrophy  
[http://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=70](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=70)
- Washington University, St. Louis: Neuromuscular Disease Center: spinal muscular atrophy  
<http://neuromuscular.wustl.edu/synmot.html#sma5q>

### Patient Support and Advocacy Resources

- Claire Altman Heine Foundation  
<http://clairealtmanheinefoundation.org/>
- Cure SMA  
<http://www.curesma.org/>
- Muscular Dystrophy Association  
[https://www.mda.org/sites/default/files/publications/Facts\\_SMA\\_P-181.pdf](https://www.mda.org/sites/default/files/publications/Facts_SMA_P-181.pdf)
- National Organization for Rare Disorders (NORD)  
<https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/>
- Spinal Muscular Atrophy Foundation  
<http://www.smafoundation.org/>

### GeneReviews

- Spinal Muscular Atrophy  
<https://www.ncbi.nlm.nih.gov/books/NBK1352>
- Spinal Muscular Atrophy, X-Linked Infantile  
<https://www.ncbi.nlm.nih.gov/books/NBK2594>

### ClinicalTrials.gov

- ClinicalTrials.gov  
<https://clinicaltrials.gov/ct2/results?cond=%22spinal+muscular+atrophy%22>

### Scientific Articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Muscular+Atrophy,+Spinal%5BMAJR%5D%29+AND+%28spinal+muscular+atrophy%5BTI%5D%29+AND+review%5Bpt%5D+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D>

### OMIM

- SPINAL MUSCULAR ATROPHY, LATE-ONSET, FINKEL TYPE  
<http://omim.org/entry/182980>
- SPINAL MUSCULAR ATROPHY, LOWER EXTREMITY-PREDOMINANT, 1, AUTOSOMAL DOMINANT  
<http://omim.org/entry/158600>
- SPINAL MUSCULAR ATROPHY, TYPE I  
<http://omim.org/entry/253300>
- SPINAL MUSCULAR ATROPHY, TYPE II  
<http://omim.org/entry/253550>

- SPINAL MUSCULAR ATROPHY, TYPE III  
<http://omim.org/entry/253400>
- SPINAL MUSCULAR ATROPHY, TYPE IV  
<http://omim.org/entry/271150>
- SPINAL MUSCULAR ATROPHY, X-LINKED 2  
<http://omim.org/entry/301830>

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